Exhibit I

ERYTHROPOIETIN, NITRIC OXIDE SYNTHASE AND RESISTANCE TO MYOCARDIAL ISCHEMIA

Rabbits adapted to chronic hypoxia exhibit increased resistance to myocardial ischemia, resulting from increased nitric oxide production from endothelial nitric oxide synthase (1). However, the sensor responsible for detecting hypoxia resulting in increased nitric oxide production is unknown. The adequacy of renal tissue oxygenation at Epo-producing sites regulates Epo production (2), but a more potent extrarenal oxygen sensor may exist (3). L-NAME partially blocks increase in plasma levels of Epo in mice following exposure to hypoxia, thus implicating nitric oxide in oxygen sensing and Epo production (4). Epo directly stimulates atrial natriuretic peptide secretion from adult rat atria but not cultured myocyte (5). These data suggest Epo may play a role in adaptation of hearts to chronic hypoxia and resistance to ischemia by a NOS related mechanism.

Hypothesis 1: Chronic hypoxia results in increased Epo production that subsequently controls nitric oxide production from NOS.

1. Measure Epo receptors in normoxic and hypoxic hearts.
   Availability of antibody to Epo

Hypothesis 2: Epo increases nitric oxide production from NOS3.

2. Treat normoxic rabbits acutely with Epo, is there an increase in nitric oxide production resulting in cardioprotection.

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